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CORRELATION BETWEEN NEUTROPHIL/LYMPHOCYTE RATIO AND DEPRESSION SEVERITY DEGREE IN PATIENT WITH CHRONIC KIDNEY DISEASE ON REGULAR HEMODIALYSIS AT H. ADAM MALIK GENERAL HOSPITAL MEDAN

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ABSTRACT The objective of this study was to find the correlation between neutrophil/lymphocyte ratio (NLR) and depression severity in patient with chronic kidney disease (CKD) on regular hemodialysis. This was a cross sectional study on 78 patients with CKD on regular hemodialysis at H. Adam Malik General Hospital Medan diagnosed with depression using Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria and Beck Depression Inventory-II (BDI-II) score between November 2017 to February 2018. Data analysed using SPSS with Spearman and Kruskal Wallis correlation tests. Confidence interval of 95% was used and p value <0.05 was considered statistically significant. Result shows positive significant correlation between NLR and depression severity degree in CKD patients on regular hemodialysis at H. Adam Malik General Hospital with coefficient correlation value 0.313 and p <0.05.

KEYWORDS : neutrophil/lymphocyte ratio, depression severity degree, BDI-II score.

INTRODUCTION

Depression is a general mental disorder characterized by sadness, loss of happiness,guilty feeling, loss of concentration, sleep deprivation, change of appetite ,and low energy. This problem can become chronic or repeated (50-65%) and it also can adversely affect daily activities. In severe cases, depression can cause someone to commit suicide.[1,2] Depression causes significant impact on global health and is estimated to affect 350 millions peoples. Depression disorder more common to afflict young adults and this causes reduce of their proper function in communities. World Health Organization (WHO) predicts that depression will become second highest morbidity rate all around the world in 2020.[3,4,5]

Depression has been correlated with some changes in the central nervous system, immune response and vascular reactivity in which all factor contribute to activate sistemic inflammatory response.[6,7] Stress and depression may elevate neutrophil count and decrease lyphocyte count.[8] Inflammatory response also correlated with other chronic diseases like malignancy, diabetes mellitus, hypertension, chronic kidney disease, cardiovascular disease ,and psychiatry disorder. White blood cell and its subtype are predictors for chronic inflammation. Neutrophil and leucocytes are important in inflammatory process.[3]

Chronic kidney disease (CKD) is a irreversible and progressive failure condition of kidney where our body fail to maintain metabolism and electrolyte balance and causes uremic, metabolic acidosis,anemia, electrolyte imbalance and endocrine disorders. The main etiologies for CKD are diabetes, hypertension, glomerulonephritis, and polycystic kidney disease. Hemodialysis is a method for CKD treatment. In the other hands, hemodialysis also affects in patients quality of life both physically and psycologically.[4] Patients with CKD usually have neuropsichiatric complication and depression is one of the most important disorder because of its high prevalence, potentially high mortality and cause a decrease in quality of life.[9]

Many biomarkers have been searched to evaluate inflammatory process in patient with depression and CKD. Neutrophil/lymphocyte ratio (NLR) has been a great indicator for inflammation. Isaac et al. In his research said that evelated level of NLR correlated with mortality rate in patient with multiple chronic conditions.[10] NLR has been reported as an good indicator for inflamation status and this ratio has been used for some diseases including psichiatry disorder like schizophrenia and alzheimer disease. In this studies, the results were concluded that there were high NLR groups compared with healthy subjects.[8,11] Some studies also reported the correlation between NLR with depression. Aydin et al. In his study at 2016 showed that the more severe depression condition , the higher NLR count (r = 0.333, p<0.001)[3]. Demir et al. also reported significant NLR differences in patient with major depression and control subjects with p=0.044 , but it failed to show the correlation between depression severity degree and increased NLR count.[8]

METHODS

Patient Selection

This study was an analytics cross sectional study on 132 patients in regular hemodialysis (age $\geq$18 years old) in H. Adam Malik General Hospital, Medan, Indonesia between November 2017 – February 2018 to identify correlation between neutrophil/lymphocyte ratio and severity level of depression. The sample was taken consecutively in which the patients with included criterias collected until sampling quantity achieved. Written informed consent were signed by all participants before included to the study.[12]

Diagnosis of depression

All particiants went through history taking (age, gender, marrital status, job, and level of education) and questioned with 21 questions in Beck Depression Inventory (BDI) questionnaire and Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria to diagnose depression. Another test to complete was hematology series to count NLR berfore hemodialysis started.

Data analysis

Data analysed using SPSS with Spearman and Kruskal Wallis correlation tests. Confidence interval of 95% was used and p value <0.05 was considered statistically significant.

RESULTS

Among 132 patients on regular hemodialysis in H. Adam Malik General Hospital, 119 patients approved to join the study. There were 13 patients excluded in this study because of their conditions such as their conciousness state, on antidepressants drugs, had acute infections, and patients who refused to take part of this study. Another 21 patients excluded because they did not meet the DSM-5 criteria for depression. Total 98 patients approved by DSM-5 criteria ,filled BDI II questionnaire and had their blood drawed for routine hematology evaluation. There were 18 patients with BDI-II score 0-13 and 2 patients with extremely high NLR possibly had an acute infection. From 78 patients (59.09% patients on regular hemodialysis) with BDI-II score ≥14, 37 patients had mild depression, 34 patients with moderate depression and 7 patients had severe depression all included in this study.

Characteristics of subjects in this study described as seen in table 1 included gender, age, level of education, job, marital status, and BDI score for depression.

Table 1. Characteristics of subjects (CKD patients on regular hemodialysis) with depression

Characteristics	n (%)
Gender [a]	
Female	21 (26.9)
Male	57 (73.1)
Age,years,median (min-max.)b	55 (20 – 77)
< 60 years old a	53 (67.9)
> 60 years old	25 (32.1)
Education [a]	
Junior high school	25 (32.1)
High school	33 (42.3)
Diploma/bachelor	20 (25.6)
Job [a]	35 (44.9)
Enterpreneur	18 (23.1)
Housewife	13 (16.7)
Civil officer	9 (11.5)
Retired	2 (2.6)
Midwife	1 (1.3)
Pastor	
Marital status[a]	8 (10.3)
Single	70 (89.7)
Married	
Score BDI, median (min-max)[b]	20,5 (14 – 39)
Mild depression a	37 (47.4)
Moderate depression	34 (43.6)
Severe depression	7 (9)

[a]Cathegorical data: n(%)
[b]Numerical data, data distibution was not normal: median (min-max.)

As we see the table above we can conclude that there was 78 subjects in this study. It also describe the characteristics patients in this study. There was more male subjects than female subjects, age <60 years old more than the older one, most of them were high school graduated, married, and most of them were enterpreneur. Depression severity degree showed that most of the subjects had mild depression (47.4%) followed by moderate depression with 34 subjects (43.6%).

Table 2 described routine hematology evaluation in this study. Mean hemoglobin level was 9.08 ± 1.53 g/dl, leukocytes $7.394.1 \pm 2.423,97$ /mm^3, thrombocyte $211.871,79 \pm 80.332,65$ /mm^3, neutrophil 64.85 ± 12.28 %, lymphocyte 20.61 ± 7.9%, and neutrophil/lymphocyte ratio 3.31 (1.01 ± 14.33).

Table 2. Hematology results characteristics

Variable	n (%)
Hb, mean + SD, g/dL	9.08 +1.53
Leukocyte, mean + SD, /mm3	7,394.1 +2,423.97
Trombocyte, mean + SD, /mm3	211,871.79 + 80,332.65
Neutrophil, mean + SD, %	64.85 + 12.28
Lymphocyte, mean + SD, %	20.61 + 7.9
Neutrophil/lymphocyte ratio, median (min-max)	3.31 (1.01 + 14.33)

Table 3 showed correlation between demographic characteristics and depression severity degree where the variable characteristics such as gender, age, level of education and marital status had no significant relation with depression severity degree.

Table 3. Correlation between demographic characteristics and depression severity degree in patients with CKD on regular hemodialysis.

Variable	Depression			Total n (%)	p
	Severe n (%)	Moderate n (%)	Mild n (%)		
Gender					0.278

Female	4 (19%)	11 (52.4%)	6 (28.6%)	21	
Male	3 (5.3%)	23 (40.4%)	31 (54.4%)	57	
Age					1.000
<60 years old	5 (9.4%)	23 (43.4%)	25 (47.2%)	53	
> 60 years old	2 (8%)	11 (44%)	12 (48%)	25	
Level of education	2 (8%)	12 (48%)	11 (44%)	25	1.000
Junior High school	5 (9.4%)	22 (41.5%)	26 (49.1%)	53	
High school and univerity					
Marital status	4 (50%)	2 (25%)	2 (25%)	8	0.086
Single	3 (4.3%)	32 (45.7%)	35 (50%)	70	
Married					

Difference level of neutrophil/lymphocyte ratio in depression severity degree in patient with CKD on regular hemodialysis described in table 4 below. This table described that there was a significance difference in NLR in 3 depression severity degree . NLR was higher in severely depressed patients compared with mild and moderate depression, but no significant differences between mild and moderate depression.

Table 4. Differences neutrophil/lymphocyte ratio in depression severity degree in patients with CKD on regular hemodialysis

Depression severity degree	neutrophil/lymphocyte ratio median (min – max)	p
Mild	2.62 (1.01 – 9.54)#	0.002*
Moderate	3.56 (1.07 – 14.33)#	
Severe	6.56 (4.46 – 10.46)	

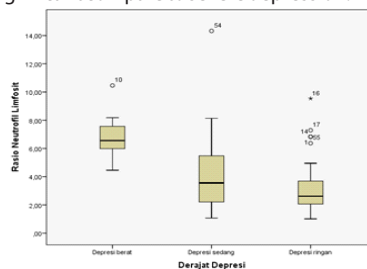*p <0.05, # significant compare to severe depression.

Figure 1. Neutrophil/lymphocyte ratio boxplot diagram and its correlation with depression severity degree

Tabel 5 and picture 2 below showed that there was a significant relation between depression severity degree with BDI-II score and NLR with coefficient correlation score 0.313 and p<0.05. So that the higher BDI-II score, the higher neutrophil/lymphocyte ratio.

Table 5. Correlation between BDI-II score and neutrophil/lymphocyte ratio

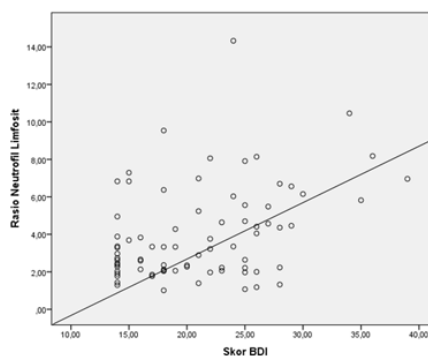|	p	r
BDI-II score Neutrophil/Lymphocyte Ratio	0.005*	0.313

*p <0.05

Figure 2. Scatter dot diagram between BDI-II score and neutrophil/lymphocyte ratio

DISCUSSION

From this study, depression prevalence in patient with CKD on regular hemodialysis at H. Adam Malik General Hospital was 78 patients from total patients on regular hemodialysis. AlDukhayel in his study at Saudi Arabia also found that there was high depression prevalence in hemodialysis patients. Study from Ravaghi et al also found the same high prevalence for depression in patient with CKD on hemodialysis [13]. Depression was more frequent in male subjects (73.1 %) than female subjects (26.9%). This finding also reported in AlDukhayel study that male patients with CKD on hemodialysis had higher depression prevalence than female patients.[15] Otherwise, WHO and Deshpande et al found different results where women were more susceptible to stress. Prolonged stress made women more sensitive to relationship problems at home and at working places.[5,15]

Majority subjects in this study had mild depression (37 patients, 47.4%), only seven patients had severe depression. The same result found in Kimmel et al study where mild depression was the highest prevalence (25%) and diagnosed using BDI score for depression. However, Thomas et al in his study uses Zung Self-rating Depression Scale (ZSDS) method for depression evaluation shows highest moderate depression prevalence (76.47%) in CKD patients on hemodialysis.[16]

NLR is a simple parameter and easy to evaluate. There is no cut-off value approved to differentiate normal and abnormal value in NLR evaluation.[17] Some studies categorize NLR in interval and some others use certain cut-off value.[18] NLR is a ration between cells that mediated different type of immunity. Neutrophil represents first-line immunity that has phagocytic and apoptosis activity by secreted inflammatory mediators especially cytokines. [19] Inflammatory response elicited by cytokines induct more inflammatory response because of dysfunctional cells and oxidative stress. In the other hand, lymphocytes functioned as protecting and managing specific inflammation. Low lymphocytes count mirrors bad health conditions and physiological stresses.[20] NLR also said to be beneficial to detect an inflammatory response, to show stress intensity, systemic inflammation, and cascade cytokines that related to depression. Inflammatory cytokines such as IL-2, IL-6, TNF, MCP1, and P-selectin raise in depression. These inflammatory cytokines mediate changes in neurotransmission, especially in 5-HT synthesis and metabolism process that trigger dysfunctional synaptic plasticity in depression state.[17]

Mean neutrophil count in this study was $64.85 \pm 12.28\%$, where it's still in normal range, and so is Lymphocytes count ($20.61 \pm 7.9\%$). Median score for neutrophil lymphocytes ratio was 3.31 (1.01 – 14.33) and for BDI-II score was 20.5 (14 – 39) and categorized as moderate depression. These findings probably because of multifactorial etiology in causing depression, not only NLR but also from other factors divided into two categories that is biological and behavioral, where behavioral factors included disease burden, self-care, functional disturbance, treatment adherence, lack social support, and bad quality of life. Biological factors included other comorbid diseases, inflammation, changes in autonomic neural activity, hormonal changes, and genetics.[21] However, in this study, there was significant NLR difference among depression severity degree (p=0.001), where patients with severe depression had higher NLR than those with mild and moderate depression. This finding had the same finding with Aydin et.al study in 256 patients with depression using HAM-D score that showed severe depression had higher NLR than mild and moderate depression (1.91 ± 0.85 vs 1.42 ± 0.53, p <0.001).[3] Demie et al study in 41 depression patients and 47 control patients using BDI score stated that there was significant NLR difference in depression patients compare with control patients (p=0.044), but this study failed to show significant differences between depression severity degree.[8]

This study shows positive significant correlation between BDI score and NLR in CKD patients on regular hemodialysis with correlation coeficient score 0.313 and p score <0.05. This fact explains that higher BDI-II score shows higher NLR. Aydin at al. study also stated positive significant correlation between depression severity degree and increase NLR (r=0.333, p<0.001). That study also stated NLR is a independence predictor for severe and very severe depression (odds ratio: 3.02, confidence interval 95%: 1.867-4.884, p <0.001) and ROC analysis determines NLR cut-off to predict severe and very severe depression with 61.4% sensitivity and 61.2% specificity.[3] However, those findings had different result with Demir at al study that stated there was no significant correlation between depression severity degree and increased NLR (r=0.138, p= 0.391).

Limitations in this study was a cross-sectional study that only determined the correlation between variables without causal correlation. Minimal sample size also limited this study. Some other important aspects for depression evaluation including family history, social background, duration of hemodialysis, and other factors that were not evaluated.

CONCLUSION

This study showed a positive significant correlation between NLR and depression severity degree in CKD patients on regular hemodialysis at H. Adam Malik General Hospital with coefficient correlation value of 0.313 and p <0.05. Depression prevalence in CKD patients on regular hemodialysis at H. Adam Malik General Hospital is high (59.09%) with 47.4% mild depression, 43.6% moderate depression, and 9% severe depression. Median value for neutrophil/lymphocyte ratio in this study was 3.31 (1.01 – 14.33).

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